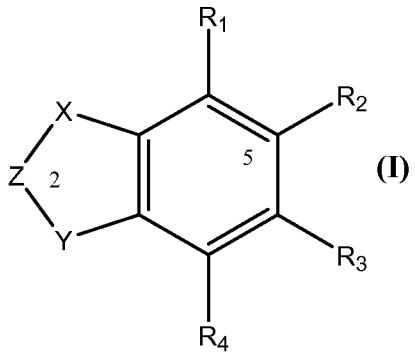
Claims Listing

1. (Previously presented) A method of inhibiting activity of MIF comprising contacting MIF with an MIF activity-inhibiting effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof



(I)

wherein

X is—$N(R_6)$—;

Y is—$N(R_7)$—;

Z is—C(O)—;

R_1 is selected from hydrogen, or $(CR_5R_{5'})_n$halo;

R_2 is selected from the group consisting of C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $(CR_{12}R_{12'})_mC(O)R_8$, $(CR_{12}R_{12'})_mC(S)R_8$, $(CR_{12}R_{12'})_mS(O)R_8$, $(CR_{12}R_{12'})_mS(O)_2R_8$, $(CR_{12}R_{12'})_mOR_9$, $(CR_{12}R_{12'})_mSR_9$, $(CR_{12}R_{12'})_nNR_{10}R_{11}$, $(CR_{12}R_{12'})_mC(=NR_{24})R_{22}$ and $(CR_{12}R_{12'})_mR_{13}$;

R_3 is selected from hydrogen, C_1-C_6alkyl, $(CR_{16}R_{16'})_pNR_{14}R_{15}$, $(CR_{16}R_{16'})_pOR_{17}$, $(CR_{16}R_{16'})_p$halo, and $(CR_{16}R_{16'})_pNO_2$

R_4 is hydrogen, or halogen;

Each R_5 and R_5 is independently hydrogen,

R_6 is hydrogen, or C_1-C_3alkyl;

R_7 is hydrogen or C_1-C_3alkyl;

R_8 is selected from the group consisting of hydrogen, C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, OR_{19}, SR_{19}, $N(R_{20})_2$, $[NH—CH(R_{21})—C(O)]_q—OR_{29}$, pyranosyl and $(CR_{12}R_{12'})_tR_{13}$;

R_9 is hydrogen;

R_{10} and R_{11} are independently selected from hydrogen, and $C(O)R_{23}$;

Each R_{12} and $R_{12'}$ is independently hydrogen;

R_{13} is selected from OR_{25}, SR_{25}, halo, $N(R_{25})_2$, and $C(O)R_{31}$;

R_{14} and R_{15} are each hydrogen;

Each R_{16} and $R_{16'}$ is hydrogen;

R_{17} is hydrogen;

R_{19} and each R_{20} are independently selected from hydrogen, C_1-C_{20}alkyl, and, $(CR_{26}R_{26'})_tR_{27}$;

R_{21} is the characterising group of an amino acid wherein the amino acid is alanine, phenylalanine, serine, homoserine or norvaline;

R_{22} is $NH(C_{1\text{-}6}alkyl)$;

R_{23} is $(CR_{26}R_{26'})_tR_{27}$;

Each R_{24} is independently selected from hydrogen and C_1-C_6alkyl;

Each R_{25} is independently selected from hydrogen, and C_1-C_6alkyl;

Each R_{26} and $R_{26'}$ is independently hydrogen;

R_{27} is selected from, OR_{30}, SR_{30}, and aryl;

Each R_{29} is independently selected from hydrogen and C_1-C_3alkyl;

Each R_{30} is independently selected from, C_1-C_3alkyl, and heterocyclyl;

R_{31} is heterocyclyloxy;

n is 0 or an integer from 1 to 3;

m is 0 or an integer from 1 to 20;

p is 0 or an integer from 1 to 6;

q is an integer from 1 to 5;

t is an integer from 1 to 10;

wherein alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

2. (Previously presented) A method according to claim 1 wherein X is—N(H)—, Y is —N(H)—, and Z is —C(O)—.

Claims 3 - 17 (Cancelled)

18. (Original) A method according to claim 1 wherein the compound of formula 1 is selected from the group consisting of: benzimidazole-2-one-5-n-pentanoate, 5-[2-(1-oxy-2-hydroxyethyl)ethyl]benzimidazol-2-one-5-carboxylate, benzimidazole-2-one-5-methanoate, benzimidazole-2-one-5-ethanoate, 3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]tetrahydro-2H-pyran-2-yl-benzimidazole-2-one-5-carboxylate, 5-bromo-6-methylbenzimidazol-2-one, 5-hydroxy-6-methylbenzimidazol-2-one, 5-dodecanylbenzoimidazol-2-one, 4,5,7-tribromo-6-methylbenzimidazol-2-one, 4,5,6,7-tetrabromobenzimidazol-2-one, 5-methyl-6-nitrobenzimidazol-2-one, 5-amino-6-methylbenzimidazol-2-one, N-(6-methylbenzimidazol-5-yl)-2-pyrimidin-2-yl-sulfanyl-acetamide, pentyl-benzimidazol-2-one-5-carbothioate, 5-(benzimidazol-2(3H)-one-6-yl)-5-oxopentanoic acid, 2(3H)-benzimidazolone-5-sulfonic acid pentyl ester, 2(3H)-benzimidazolone-5-sulfonic acid pentyl amide, N-butyl-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboximidamide, 5-heptanoylbenzofuran-2(3H)-one, methyl 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}propanoate, 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}propanoic acid, methyl 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoate, 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoic acid, and N-(3,4-dihydroxyphenethyl)-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboxamide.

19. (Currently amended) A method of treating~~, or diagnosing~~ rheumatoid arthritis wherein MIF activity is implicated comprising the administration of a treatment~~, or diagnostic~~ effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof to a subject in need thereof.

Claims 20-22. (cancelled)

23. (Original) A method of claim 19 wherein the subject is a human subject.

Claims 24-25. (cancelled)

26. (Previously presented) A method of treating rheumatoid arthritis wherein MIF activity is implicated comprising: administering to a mammal a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof and a second therapeutic agent.

27. (original) A method according to claim 26 wherein the second therapeutic agent is a glucocorticoid.

28. (Previously presented) A method of treatment of rheumatoid arthritis for which treatment with a glucocorticoid is indicated, said method comprising: administering to a mammal a glucocorticoid and a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

29. (Previously presented) A method of treating a steroid-resistant rheumatoid arthritis comprising: administering to a mammal a glucocorticoid and a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

Claims 30-40. (Cancelled)

41. (Previously presented) A method according to claim 1 wherein

R_1 is hydrogen or $(CR_5R_{5'})_n$halo;

R_2 is selected from C_{1-20}alkyl, $(CR_{12}R_{12'})_mC(O)R_8$, $(CR_{12}R_{12'})_mS(O)_2R_8$, $(CR_{12}R_{12'})_nNR_{10}R_{11}$, $(CR_{12}R_{12'})_mC(=NR_{24})R_{22}$ and $(CR_{12}R_{12'})_mR_{13}$;

R_3 is selected from hydrogen, C_{1-6}alkyl, $(CR_{16}R_{16'})_pNR_{14}R_{15}$, $(CR_{16}R_{16'})_pOR_{17}$, $(CR_{16}R_{16'})_p$halo and $(CR_{16}R_{16'})_pNO_2$;

R_4 is hydrogen or halogen;

Each R_5 and $R_{5'}$ is independently hydrogen;

R_8 is selected from C_1-C_{20}alkyl, OR_{19}, SR_{19}, $N(R_{20})_2$, $[NH\text{-}CH(R_{21})\text{-}C(O)]_q\text{-}OR_{29}$, pyranosyl and $(CR_{12}R_{12'})R_{13}$;

R_9 is hydrogen;

R_{10} and R_{11} are independently selected from hydrogen and $C(O)R_{23}$;

Each R_{12} and $R_{12'}$ is independently hydrogen;

R_{13} is selected from OR_{25}, SR_{25}, halo, $N(R_{25})_2$ and $C(O)R_{31}$;

R_{14} and R_{15} are each hydrogen;

Each R_{16} and $R_{16'}$ is hydrogen;

R_{17} is hydrogen;

R_{19} and each R_{20} are independently selected from hydrogen, C_1-C_{20}alkyl, and $(CR_{26}R_{26'})_tR_{27}$;

R_{21} is the characterising group of phenylalanine or serine;

R_{22} is $NH(C_{1-6}$alkyl);

R_{23} is $(CR_{26}R_{26'})_tR_{27}$;

Each R_{24} is independently selected from hydrogen and C_1-C_6alkyl;

Each R_{25} is independently selected from hydrogen and C_1-C_6alkyl;

Each R_{26} and $R_{26'}$ is independently hydrogen;

R_{27} is selected from OR_{30}, SR_{30} and aryl;

Each R_{29} is independently selected from C_1-C_3alkyl and heterocyclyl; and

R_{31} is heterocyclyloxy.

42. (Previously presented) A method according to claim 41 wherein

n is 0;

m is 0;

p is 0;

q is 0; and

t is 1 or 2.

43. (Previously presented) A method according to claim 1 wherein the compound of formula (I) is benzimidazole-2-one-5-n-pentanoate.